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October 22, 1999

Documents Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane.
Rm 1061
Rockville, MD 20852

Re: Docket Number 99N-2100

Dear Sir or Madam:

Procter & Gamble Pharmaceuticals has reviewed the Draft Guidance for Industry, ANDAs: Blend Uniformity Analysis. We appreciate the intent of this guidance and the effort that went into preparing it. At first pass, it appears logical that analyzing the blend for uniformity before the final dosage form is manufactured would help ensure uniformity of the final product. However, the guidance fails to address the technical problems inherent in sampling a blend to perform uniformity analysis. In addition, it does not allow for better alternatives to blend uniformity analysis, such as development of robust processes, to ensure that finished products routinely meet relevant uniformity requirements. It is our position that routine blend uniformity analysis for most products adds to manufacturing complexity, increases the risk of erroneously failing acceptable batches, and may increase the safety risks to operators of the manufacturing process, but does not significantly increase the probability of manufacturing an acceptable final product. Specific comments are provided below.

1. The technical inadequacies of available techniques for obtaining blend samples of one to three times the unit dose weight are well documented (PDA Journal of Pharmaceutical Science and Technology, Vol. 51, S. 3, Technical Report No. 25, Blend Uniformity Analysis: Validation and In-Process Testing, (1997), 5-10; Muzzio, F.J. et al, Sampling Practices in Powder Blending, Int. J. Pharm, 155 (1997) 153-78). For most products it is very difficult, if not impossible, to obtain representative samples on the order of a dosing unit, from a batch that may be more than one million times bigger than that. Use of sampling spears has been shown to produce biased samples in many instances. In P&GP's experience, these techniques often produce quite variable results which are dependent on the technique of the operator. The bias and variability introduced by sampling has the potential to cause rejection of acceptable blend. Any attempt to "reblend" based on these erroneous results really amounts to relying on probability to eventually produce the result that you want.

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2. Many processes can be shown to produce uniform product through appropriate development studies and process validation. Clearly, the product sampling plans for these experiments must be robust, to establish the process produces uniform product.. However, with appropriate experimental design, it is possible to establish the reliability of the process. If blend uniformity testing is to be used in any instance, its use should not be based on arbitrary criteria like a 50 mg dose and 50% of the blend, but should only be required when the process cannot be shown to reliably produce uniform product through appropriate development studies and process validation.

3. The sampling problems notwithstanding, testing for blend uniformity in the blender while there could be further unit operations that influence the uniformity of the product raises questions about the usefulness of the data.

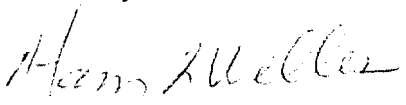
4. In instances where blend uniformity analysis is required, a scientifically valid, two tiered-approach should be developed rather than rely on the one-tiered approach suggested by FDA.

5. For potent drugs, manufacturing systems are often designed to contain the drug throughout the manufacturing process. Sampling for BUA would require breaking containment and increasing the risk of operator exposure to the drug.

6. Finally, it is our understanding that PQRI intends to address the issue of blend uniformity analysis. We recommend that this guidance be placed in abeyance until that work can be completed.

If there are any questions or if I can be of further assistance, feel free to call on me. My phone number is 513-622-3914 and my email address is welles.hl @pg.com.

Sincerely,



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